REMARKS

The Present Invention

The present invention is directed to a "humanized" polynucleotide vector, related compositions and kits, a composition for inducing an immune response, a method for expressing at least one target antigen or antigenic epitope thereof, a method for stimulating a specific immune response to at least one target antigen or antigenic epitope, and a method of making a humanized polynucleotide vector.

The Pending Claims

Claims 1-33, 36-44 and 60-110 are currently pending. Claims 1-15, 60-64, 66-77 and 105-109 are directed to the polynucleotide vector, whereas claims 27, 28, 89 and 90 are directed to the related compositions, claims 29-33 and 91-95 are directed to the kits, claims 16-22 and 78-84 are directed to the composition for inducing an immune response, claims 23-26, 65, 85-88 and 110 are directed to the method for expressing at least one target antigen or antigenic epitope thereof, claims 36-43 and 96-103 are directed to the method for stimulating a specific immune response, and claims 44 and 104 are directed to the method of making a humanized polynucleotide vector.

The Office Action

The Office has maintained the election of species requirement as set forth in the Office Action dated September 13, 2001. Claims 1-33, 36-45 and 60-65 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not satisfying the written description requirement. Claims 1-33, 36-45 and 60-65 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Claims 1-33, 36-45 and 60-65 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1-3, 7, 10, 16-19, 23-31, 36-37, 41-44 and 65 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Roop et al. (U.S. Patent No. 6,143,727). Claims 1-3, 7-9, 15, 27, 29 and 30 have been rejected under 35 U.S.C. § 102 (e) as allegedly anticipated by Carrano et al. (U.S. Patent No. 6,197,755). Claims 1-3, 7-9, 15-21, 23-31, 36, 37 and 41-44 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of and, therefore, unpatentable over Carrano et al. as applied to claims 1-3, 7-9, 15-21, 27, 29, 30, 36, 37 and 41-44, and further in view of Eastman et al. (U.S. Patent No. 6,103,407). Claims 1-3, 7-9, 15-21, 23-31, 36, 37 and 41-44 have been rejected under 35 U.S.C. §103(a) as allegedly obvious in view of and, therefore, unpatentable over Carrano et al. and Eastman et al. as applied to claims 1-3, 7-9, 15-21, 23-31, 36, 37 and 41-44 in further view of Zurr et al. (U.S. Patent No. 5,648,235). Claims 1-3, 7,

10, 16-19, 23-31, 36-44 and 65 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious in review and, therefore, unpatentable over Roop et al. as applied to claims 1-3, 7, 10, 16-19, 23-31, 36-38, 41-44 and 65 in further view of Danko et al. (Gene Ther. 1:114-121 (1994)). Reconsideration of these rejections is hereby requested.

The Amendments to the Specification, Claims and Abstract

The specification has been amended to recite the priority claim. As required by 37 CFR § 1.72(b), an abstract has been incorporated into the application. Sequence identification numbers have been assigned to the sequences set forth in lines 10 and 12 on page 19. Assignment of a sequence identification number to the combined representation of primers 1 and 2 on page 47 is unnecessary inasmuch as a sequence identification number already has been assigned on page 48. Claims 34, 35 and 46-51 have been canceled as directed to a non-elected species. Claim 45 also has been canceled without prejudice to reinstate. Applicants reserve the right to pursue any canceled subject matter in a continuation, continuation-in-part, divisional, or other application. Cancellation of any subject matter should not be construed as abandonment of that subject matter. Claims 6, 25 and 42 have been amended to correct obvious typographical errors. Claim 12 has been amended to address matters of form. The phrase "target products" has been deleted from claims 1, 15, 16, 20, 23, and 44. The term "pharmaceutical" has been deleted from claims 27 and 28. The phrase "polynucleotide vector vaccine" has been deleted from claims 16-22, 30, 36 and 38. The phrase "[a] composition for inducing an immune response against at least one target antigenic epitope vector" has been added to claims 16-22 and is supported by the specification in Table 1, for example. Claims 66-110 have been added and are supported by specification at, for example, pages 8-25.

No new matter has been added by way of these amendments. Separate documents setting forth the precise changes to the specification, claims, and abstract, as well as the text of all pending claims, are enclosed herewith, along with an "Abstract."

Discussion of Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-33, 36-45 and 60-65 (claim 45 having been canceled) have been rejected under Section 112, first paragraph, for allegedly lacking enablement. The Office contends that the specification is not reasonably enabling for stimulating a specific immune response using a humanized polynucleotide vector comprising any human derived promoter or mammalian homolog thereof, any human-derived 3' splice sequence, and any human-derived poly A sequence. The Office argues that the specification is silent with respect to the effects of other humanized promoter combination vectors in

stimulating an immune response. This rejection is traversed for the reasons set forth below.

While the Office states that the rejected claims are not enabled for stimulating a specific immune response using a humanized polynucleotide vector other than the polynucleotide vector pITL, Applicants note that claims 1-33, 44, and 60-64 are not even directed to a method of stimulating a specific immune response. Rather, claims 1-15 and 60-64 are directed to humanized polynucleotide vectors, claims 16-22, 27 and 28 are directed to related compositions, claims 29-33 are directed to related kits, claim 44 is directed to a method of making a humanized polynucleotide vector, and claims 23-26 and 65 are directed to a method of expressing at least one target antigen or antigenic epitope thereof in cells. Nowhere in the Office Action has the Office established that Applicants have not enabled the vectors, composition, kits, method of making the vector, and method of expressing at least one target antigen or antigenic epitope thereof in cells.

Regarding claims 36-43, the only claims directed to a method of stimulating an immune response, Applicants point out that the instant specification teaches how to make the humanized polynucleotide vectors at, for example, page 8, line 30, through page 22, line 21, and Examples 1-3, 10 and 11. The instant specification teaches how to use the vectors at, for example, page 22, line 22, through page 25, line 17, and Examples 4-9. Applicants also direct the Office's attention to the myriad of human promoters known in the art (*see*, for example, Ohlsson et al., *Int. J. Dev. Biol.*39(5): 869-876 (1995) and Forstermann et al., Naunyn Schmiedebergs Arch Pharmacol 352(4): 351-64 (1995) (both of which are attached hereto)), as well as the numerous 3' splice sequences known in the art (*see*, for example, Blumenfeld et al., *Hum. Mutat.* 6(3): 199-209 (1995) and Tuchman et al., *Hum. Mutat.* 2(3): 174-8 (1993) (both of which are attached hereto)), and the Declaration under 37 C.F.R. § 1.132 of Edward Nelson (attached hereto). As for human derived poly A sequences, a poly A sequence is a poly A sequence – it's as simple as that. DNA vector construction has been known in the art for many years (*see*, for example, Molecular Cell Biology, Darnell, J., 248-262 (1986); and Nischt et al., Eur. J. Biochem. 200(2): 529-536 (1991), both of which are attached hereto). Furthermore, it is known in the art that organisms or proteins associated with disease generally cause an immune response in humans as evidenced by Fiore et al. (*J. Gen. Virol.* 76 (Pt 8):1981-8 (1995), attached hereto). As such, a person of ordinary skill in the art would be enabled to the full scope of the claims based on the disclosed teachings of this application. As supported by the Declaration under 37 C.F.R. § 1.132 of Jerry E. Manning (attached hereto), the screening of various combinations of promoters and 3' sequences is a matter of routine experimentation. Routine experimentation does not constitute undue experimentation.

Furthermore, the Manual of Patent Examining Procedure (M.P.E.P.), at Section 2164.02, states that "[c]ompliance with the enablement requirement of 35 U.S.C. §112, first paragraph, does not turn on whether an example is disclosed." Therefore, the fact that the instant specification contains only one example demonstrating the immunostimulatory effects of the claimed vectors does not render the claims non-enabled.

While the Office raises gene therapy issues, such as delivery of therapeutic genes to the sites of disease and sustained expression, such issues are irrelevant to the vectors and methods of the present invention. The present invention is not directed to gene therapy and sustained expression is not only unnecessary, but can be undesirable, in the context of the claimed methods (see, e.g., Youssef et al., J. Immunol. 161 (8): 3870-3879 (1998); and Declaration under 37 C.F.R. § 1.132 of Edward Nelson (both of which are attached hereto)).

In view of the foregoing, Applicants submit that the specification is enabling for one of ordinarily skilled in the art to make and use the present invention. Therefore, Applicants hereby request that the rejection of claims 1-33, 36-44 and 60-65 for alleged lack of enablement be withdrawn.

Claims 1-33, 36-45 and 60-65 have been rejected under Section 112, first paragraph, for allegedly failing to describe adequately the claimed invention. This rejection is traversed for the reasons set forth below.

The Office contends that 1, 16, 23 and 44 recite "a human derived promoter or mammalian homolog thereof which is functional in target tissue or target cells," but the RANTES promoter is the only promoter disclosed in the specification. Applicants have sufficiently described human-derived promoters such that one of ordinary skill in the art would understand that Applicants were in possession of the claimed invention at the time the application was filed. For instance, Applicants have described in detail that the human-derived promoters are tissue-specific and allow for expression in muscle, skin, lymph nodes, epithelium, subepithelium and the like at, for example, page 16, lines 3-19. Furthermore, preferred promoters, such as those able to drive expression in professional antigen presenting cells, such as monocytes, macrophages, dendritic cells, Langerhans cells and the like, are described in detail at, for example, page 16, lines 19-23. Furthermore, Applicants point out that many human-derived promoters were known in the art at the time of filing of the provisional application to which this application claims priority. See, for example, Ohlsson et al., *Int. J. Dev. Biol.*39(5): 869-876 (1995); and Forstermann et al., Naunyn Schmiedebergs Arch Pharmacol 352(4):351-64 (1995), (both of which are attached hereto)). It is well-settled that Applicants need not describe that which is known in the art.

The Office further contends that "unique sites within an interrupted palindrome recognition sequence for restriction endonuclease "are not adequately described in the specification. Once, again, Applicants reiterate that they need not (and, as stated in the M.P.E.P., should not) describe that which is known in the art. At the time of filing of the provisional application to which this application claims priority, at least a dozen interrupted palindromic sequences were known in the art. See for example, the New England BioLabs product catalog. Furthermore, the term "unique site" would have been readily understood by one of ordinary skill in the art to mean a single restriction site in the interrupted palindromic sequence for cleavage by the restriction endonuclease. The New England BioLabs catalog page provided herewith distinctly defines the allegedly ambiguous phrase via multiple examples of restriction endonucleases and the unique sites within interrupted palindromic sequences at which they are active. According to the holding of *Martin v. Mayer*, 823 F.2d 500 (Fed. Cir. 1987), "[i]t is not required that the application describe the claim limitations in greater detail than the invention warrants. The description must be sufficiently clear that persons of skill in the art will recognize that the applicant made the invention having those limitations." *See id.* Applicants maintain that the phrase "unique sites within an interrupted palindrome recognition sequence for restriction endonuclease," would have been understood by a person of ordinary skill in the art at the time the application was filed and, therefore, need not be described further to satisfy the written description requirement of Section 112, first paragraph.

The Office still further contends that a human-derived 3' splice sequence and a human-derived poly A sequence, both of which are derived from human growth hormone, are not sufficiently described in the instant specification. Applicants assert that it was well-known in the art at the time the application was filed that human growth hormone is not alternatively spliced. Therefore, the alleged splicing variability the Office addresses does not exist. The splicing in the 3' region of human growth hormone does not differ in various cell types or for various poly A sequences (see, for example, page 16, lines 24-32, and page 17, lines 1-26). DeNoto et al. is cited in support of poly A sequences derived from human growth hormone (see, e.g., pg. 16, lines 30-31). Therefore, Applicants have adequately described the 3' splice sequence and poly A sequence of human growth hormone in the specification as filed.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under Section 112, first paragraph, for failure to describe adequately the claimed invention.

Discussion of Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-33, 36-45, and 60-65 (claim 45 has been canceled) have been rejected under Section 112, second paragraph, as allegedly indefinite for failing to point out particularly and claim distinctly the subject matter of the invention. Applicants respectfully disagree with this rejection.

The Office alleges that the phrase of claims 1, 16, 23, and 44 reciting "unique sites within an interrupted palindrome recognition sequence for restriction endonuclease," is indefinite because neither the name nor sequences of the sites are disclosed in the specification. As stated above, unique sites within an interrupted palindrome sequence were known in the art at the time the application to which this application claims priority was filed. The state of the art at that time is evident from the New England BioLabs product catalog as well as an article by Simcox et al. (*Gene* 155(1):129-30 (1995)) (abstract only) (both of which are attached hereto), describing specific sequence sites for such restriction endonucleases. In view of the foregoing, Applicants submit that the phrase "unique sites within an interrupted palindrome recognition sequence for restriction endonuclease," is definite.

The Office further alleges that the claims are indefinite because they recite the term "lacking" with respect to nucleic acid sequences encoding vector-derived polypeptides. The plain meaning of the word "lacking" is *missing or deficient* (*see Merriam-Webster Dictionary Online)*. The specification teaches what is meant by "lacking" at, for example, page 12, line 13, through page 13, line 1. Claim usage of the term "humanized vector," in conjunction with the word "lacking" is sufficiently definite to point out particularly and claim distinctly the subject matter of the claimed invention. Thus, the word "lacking" is not overly vague, such that one ordinarily skilled in the art would not be reasonably apprised of the scope of the invention.

The Office also alleges that the phrase "cDNA target products" is vague and indefinite. This allegedly indefinite phrase is defined in the specification at, for example, page 12, lines 26-27. The specification defines the phrase as rtPCR products cloned using a sequence complementary to the sequence acceptance site. In order to expedite prosecution of this application and not in acquiescence of the rejection, Applicants have removed the phrase "cDNA target products" from the claims and amended the claims to recite "cDNA derived from rtPCR... ." Support for the amended claim language can be found at, for example, page 19, lines 3-4. Furthermore, persons having ordinary skill in the art understand that rtPCR yields cDNA, and thus the claims as amended are not indefinite.

In view of the foregoing, Applicants submit that claims 1-33, 36-45 and 60-65 are definite. Accordingly, Applicants respectfully request withdrawal of the rejection under Section 112, second paragraph.

Discussion of Rejections under 35 U.S.C. § 102(e)

Claims 1-3, 7, 10, 16-19, 23-31, 36-37, 41-44 and 65 have been rejected under Section 102(e) as allegedly anticipated by Roop et al. (U.S. Pat. No. 6,147,727). This rejection is traversed for the reasons set forth below.

Applicants submit that Roop et al. does not teach a promoter operably linked to a sequence acceptance site, which directionally accepts cDNA from rtPCR cloning via unique restriction sites within an interrupted palindromic sequence, as does the present invention. Furthermore, the claimed invention is directed to a vector lacking an antibiotic resistance gene. Roop et al., on the other hand, teaches vector selection via antibiotic resistance and does not discuss the importance of minimizing vector-derived polypeptides. Therefore, Roop et al. cannot be said to teach the instantly claimed vectors (claims 1-3, 7 and 10), compositions (claims 16-19, 27 and 28), kits (claims 29-31), and methods of use (claims 23-26, 36, 37, 41-44 and 65). Accordingly, Applicants request the withdrawal of this rejection.

Claims 1-3, 7-9, 15, 27, 29 and 30 are rejected under Section 102(e) as allegedly anticipated by Carrano et al. (U.S. Pat. No. 6,197,755). This rejection is traversed for the reasons set forth below.

Applicants point out that, although Carrano et al. teaches cloning via a sequence acceptance site, the method disclosed by Carrano et al. requires two different restriction endonuclease sites at the respective ends of the PCR product. The claimed invention is distinguished from Carrano et al. in that cloning is carried out via a unique restriction site within an interrupted palindromic sequence. This method of cloning requires only one restriction endonuclease, which decreases the risk of additional and unwanted restriction sites. Furthermore, the claimed vector lacks an antibiotic resistance gene. Carrano et al., on the other hand, teaches vector selection via antibiotic resistance and does not discuss the importance of minimizing vector-derived polypeptides. In view of the foregoing, Carrano et al. cannot be said to teach the instantly claimed vectors (claims 1-3, 7-9 and 15), compositions (claim 27), and kits (claims 29-30). Accordingly, Applicants request the withdrawal of this rejection.

Discussion of Rejections under 35 U.S.C. § 103(a)

The Office has rejected claims 1-3, 7-9, 15-21, 27, 29, 30, 36, 37, and 41-44 under Section 103(a) as allegedly obvious in view of and, therefore, unpatentable over Carrano et al. in view of Eastman et al. (U.S. Pat. No. 6,103,470). This rejection is traversed for the reasons set forth below.

The Office acknowledges that Carrano et al. does not teach a vector selection marker other than antibiotic resistance. However, the Office contends that this deficiency is cured by Eastman et al. Assuming, solely for the sake of argument, that one of ordinary skill in the art would have been motivated to modify the disclosure of Carrano et al. in view of Eastman et al. as proposed by the Office, Applicants point out that Eastman et al. fails to cure the other deficiencies of Carrano et al., namely rtPCR cloning carried out via a unique restriction site within an interrupted palindrome sequence, or the importance of minimizing vector-derived polypeptides.

In view of the foregoing, the present invention cannot be said to be obvious in view of Carrano et al., in view of Eastman et al. Accordingly, Applicants request the withdrawal of this rejection.

The Office has rejected claims 1-3, 7-9, 15-21, 23-31, 36, 37, and 41-44 under Section 103(a) as allegedly being obvious in view of and, therefore, unpatentable over Carrano et al. and Eastman et al. in view of Zurr et al. (U.S. Pat. No. 5,648,235). The rejection is traversed for the reasons set forth below.

Zurr et al. discloses the use of an internal ribosomal entry site to increase selectively production of a gene of interest. Zurr et al., however, does not cure the deficiencies of Carrano et al. and Eastman et al. as noted above. Zurr et al. does not teach cloning via a unique site within an interrupted palindromic recognition sequence for a restriction endonuclease, nor does it teach a vector lacking nucleic acid sequences encoding vector-derived polypeptides. Thus, the claimed invention cannot be said to be obvious to an ordinary skilled artisan in view of Carrano et al. and Eastman et al. in further view of Zurr et al. Accordingly, Applicants request the withdrawal of this rejection.

The Office has rejected claims 1-3, 7, 10, 16-19, 23-31, 36-44, and 65 under Section 103(a) as allegedly obvious in view of and, therefore, unpatentable over Roop et al. in view of Danko et al. (Gene Ther. 1994; 1:114-121). This rejection is traversed for the reasons set forth below.

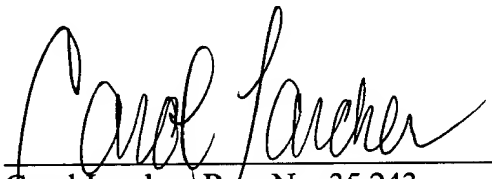
The Office acknowledges that Roop et al. does not teach the use of a myotoxic agent as an expression enhancer prior to administration of the vector composition. However, the Office contends that this deficiency is cured by Danko et al. Assuming,

solely for the sake of arguments, that one of ordinary skill in the art would have been motivated to modify the disclosure of Roop et al. in view of Danko et al. as proposed by the Office, Danko et al. fails to cure the other deficiencies of Roop et al., namely rtPCR cloning via a unique restriction site within an interrupted palindrome sequence as taught by the present invention. Additionally, the claimed vector lacks an antibiotic resistance gene, whereas Roop et al. teaches the use of an antibiotic resistance gene for selection. Accordingly, in view of the above, Applicants respectfully request the withdrawal of this rejection under Section 103(a).

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of this Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: April 25, 2003

CERTIFICATE OF MAILING

I hereby certify that this AMENDMENT AND RESPONSE TO OFFICE ACTION (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Box SEQUENCE, U.S. Patent and Trademark Office, P. O. Box 2327, Arlington, VA 22202.

Date: April 25, 2003 Sheri Page